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| DIBRINO,M | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | 9 |

**DATE MAILED:** 09/28/99

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/091,441 | Reff et al |
| **Examiner** | **Group Art Unit** |
| Marianne DiBrino | 1644 |

☒ Responsive to communication(s) filed on *Jul 19, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-39* is/are pending in the application.

Of the above, claim(s) *26-39* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4 & 5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. Applicant's election with traverse of in Paper No. 8 filed 07/19/99 is acknowledged. The traversal is on the ground(s) that the search and examination of the claims of Group I would also correspondingly identify any methods of treating or preventing conditions that are therapeutically benefitted by the inhibition of IgE expression, the claims of Group II, and that a serious burden would not be imposed on the Examiner to examine all the claims in the instant application. Regarding applicants comments about undue burden, the M.P.E.P. § 803 (July 1998) states that: "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The restriction requirement enunciated in the previous Office Action meets this criterion and therefore establishes that serious burden is placed on the Examiner by the examinatiitional Groups.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 26-37 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 8.

The invention being examined in this application is anti-human CD23 monoclonal antibodies and pharmaceutical compositions thereof.

3. Applicants are required to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, page 9 at line 10, on pages 53, 54, 55, Tables 1-5). 37 CFR 1.821(d).

4. The WO documents listed on IDS filed 07/06/99 and IDS filed 07/30/99 that are crossed out have not been considered by the Examiner because they were not submitted by Applicant. The Bonnefoy et al reference on page 3 of the IDS filed on 07/30/99 is not legible and has not been considered by the Examiner.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 12, 13 and 25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the 5E8, 6G5 and 2C8 antibodies are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines / hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

NOTE THE CURRENT ATCC DEPOSITORY ADDRESS:
American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Applicant may overcome this rejection by reciting specific variable region SEQ ID NOS in the claims instead of the antibody.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 9, 12, 13, 22 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 9 and 22 are indefinite in the recitation of " monoclonal antibody...having a binding affinity ranging from 0.01nM to 1000nM" because it is unclear what is meant since a monoclonal antibody has a binding affinity that is a discrete value rather than a range.

b. Claims 12, 13 and 25 are indefinite in the recitation of 5E8, 6G5 and 2C8 because the recitation is of the designation for a monoclonal antibody in the absence of specific reference to a deposited hybridoma.

The amendments must be supported by the specification so as not to add any new matter.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1, 3, 4, 6-8, 14, 16, 17, 19, 20 and 21 are rejected under 35 U.S.C. § 102(b) as being anticipated by Wakai et al (Hybridoma, Volume 12 (1), pages 25-43, 1993) as evidenced by references Paul et al (Fundamental Immunol., 2nd Edition, pages 705 and 870, 1989) and D'Ambrosio et al (Science, Volume 268, pages 293-297, 1995).

Wakai et al teach murine anti-human CD23 monoclonal antibodies (mAb) that inhibit IL-4 induced IgE expression by B cells in vitro using human peripheral blood mononuclear cells (PBMC)(especially page 33, first full paragraph and Table 4). Wakai et al teach said antibodies in fluid suitable for in vivo administration (especially page 28, lines 7-8). MAbs EBV-CS#2, 48.20 and MHM6 are IgG1 isotype antibodies. FcgR (Fc gamma receptors) are present on PMBC such as monocytes, macrophages, granulocytes, large granular lymphocytes as evidenced by Paul et al (especially page 705) and B lymphocytes as evidenced by D'Ambrosio et al (especially page 293, Abstract); CD23 molecules (FceRII) are present on PBMC such as monocytes, macrophages, and subpopulations of lymphocytes including B cells (especially page 870, first full paragraph) as evidenced by Paul et al. Claims 8 and 21 are included because the ability to inhibit IL-4 induced IgE expression *in vivo* is an inherent property of said antibodies because they have this property *in vitro*. Therefore, Wakai et al inherently teach murine anti-human CD23 mAbs comprising constant regions that binds to human Fc gamma receptors and inhibit IgE expression.

The reference teachings anticipate the claimed invention.

11. Claims 1, 3, 4, 6, 14, 16, 17 and 19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Saxon et al (J. Immunol., Volume 147, pages 4000-40006, 1991) as evidenced by references Paul et al (Fundamental Immunol., 2nd Edition, pages 705 and 870, 1989) and D'Ambrosio et al (Science, Volume 268, pages 293-297, 1995).

Saxon et al teach anti-CD23 mAbs 135 and 45, both of which are IgG1, that inhibit the in vitro IgE expression by human plasma cell line AF-10 (especially page 4001, "mAb and IgE-IC" section and page 4002, second full paragraph). Saxon et al teach said antibodies in a fluid suitable for in vivo administration (especially page 4000, Materials and Methods section). FcgR (Fc gamma receptors) are present on PMBC such as monocytes, macrophages, granulocytes, large granular lymphocytes as evidenced by Paul et al (especially page 705) and B lymphocytes as evidenced by D'Ambrosio et al (especially page 293, Abstract); CD23 molecules (FceRII) are present on PBMC such as monocytes, macrophages, and subpopulations of lymphocytes including B cells (especially page 870, first full paragraph) as evidenced by Paul et al. Therefore, Saxon et al inherently teach murine anti-human CD23 mAbs comprising constant regions that bind to human Fc gamma receptors and inhibit IgE expression.

The reference teachings anticipate the claimed invention.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-11 and 13-25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Wakai et al (Hybridoma, Volume 12 (1), pages 25-43, 1993) and Saxon et al (J. Immunol., Volume 147, pages 4000-40006, 1991) as evidenced by references Paul et al (Fundamental Immunol., 2nd Edition, pages 705 and 870, 1989) and D'Ambrosio et al (Science, Volume 268, pages 293-297, 1995) in view of Newman et al (U.S. Patent No. 5,658,570) and further in view of Queen et al (U.S. Patent No. 5,585,089).

Wakai et al teach murine anti-human CD23 monoclonal antibodies (mAb) that inhibit IL-4 induced IgE expression by B cells in vitro using human peripheral blood mononuclear cells (PBMC)(especially page 33, first full paragraph and Table 4). MAbs EBV-CS#2, 48.20 and MHM6 are IgG1 isotype antibodies (especially page 27, "Monoclonal antibodies" section). Wakai et al teach said antibodies in fluid that is compatible with in vivo administration (especially page 28, lines 7-8).

Saxon et al teach anti-CD23 mAbs 135 and 45, both of which are IgG1, that inhibit IL-4 induced IgE expression in vitro by human plasma cell line AF-10 (especially page 4001, "mAb and IgE-IC" section and page 4002, second full paragraph). Saxon et al teach said antibodies in fluid that is compatible with in vivo administration (especially page 4000, Materials and Methods section).

FcγR (Fc gamma receptors) are present on PMBC such as monocytes, macrophages, granulocytes, large granular lymphocytes as evidenced by Paul et al (especially page 705) and B lymphocytes as evidenced by D'Ambrosio et al (especially page 293, Abstract); CD23 molecules (FcεRII) are present on PBMC such as monocytes, macrophages, and subpopulations of lymphocytes including B cells (especially page 870, first full paragraph) as evidenced by Paul et al. Therefore, Wakai et al or Saxon et al teach murine anti-human CD23 mAbs comprising constant regions that binds to human Fc gamma receptors and inhibit IgE expression.

Wakai et al and Saxon et al do not teach anti-CD23 mAbs comprising a constant region that binds to human gamma receptors and inhibits IgE expression that are primatized or humanized, or that said mAbs have binding affinities in the range from 0.01nM to 1000nM or at least 5nM or at least 100nM. Wakai et al and Saxon et al do not teach that said mAbs are capable of inhibiting the binding of monoclonal anti-human antibody 5E8 or 6G5 to CD23.

Newman et al disclose anti-human CD23 mAbs that comprise a primate antigen binding portion and are humanized (especially Abstract, column 2, lines 56-60, column 6, line 15 and claim 8). Newman et al also disclose the advantages of said mAbs as human therapeutics, namely, that said antibodies don't suffer from: immunogenicity and induction of human anti-antibody (HAA) response upon repeated administration and relatively short half-life compared to human antibodies; in addition, they lack effector functions with human cells or complement (especially column 2, lines 26-45). Newman et al disclose pharmaceutical compositions containing said mAbs (especially column 4, lines 63-65).

Queen et al disclose humanized mAbs that have binding affinities of at least about 5nM or stronger (especially column 10, lines 57-63, i.e., at least about $10^8$ $M^{-1}$ = at least about 10nM) as well a mAb with a binding affinity of 100nM (especially column 56, lines 43). Queen et al

also disclose the advantages of such humanized mAbs (especially column 1, lines 25-67 and continuing onto column 2, lines 1-10).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have arrived at the claimed invention because of the disclosure of Newman et al of privatized and/or humanized anti-CD23 mAbs and pharmaceutical compositions, thereof, because of the teaching of Wakai et al or Saxon et al of anti-CD23 mAbs that bind to FcγRs and inhibit IgE expression, and because of the disclosure of Queen et al of mAbs that have binding affinities equal to the MAbs of the instant claims. Claims 13 and 25 are included because it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created an anti-human CD23 mAb capable of inhibiting the binding of monoclonal anti-human CD23 antibodies 5E8 or 6G5 to CD23, i.e., to create another mAb with the same binding epitope binding specificity as 5E8 or 6G5.

One of ordinary skill in the art at the time the invention was made would have been motivated to primatize and humanize the anti-CD23 mAbs of Wakai et al and Saxon et al as taught by Newman et al, particularly in light of the advantages, such as lessened immunogenicity and longer half-life, of such altered antibodies in administration to humans as therapeutics as taught by Newman et al and by Queen et al. One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the anti-CD23 mAbs of Wakai et al and Saxon et al for the anti-CD23 mAbs of Newman et al into the pharmaceutical compositions of Newman et al given the disclosure of such compositions containing primatized and humanized anti-CD23 mAbs. One of ordinary skill in the art at the time the invention was made would have been motivated to produce the anti-CD23 mAbs of the instant claims having a binding affinities ranging from 1000nM to 0.01nM, given the disclosure of Queen et al of humanized mAbs having binding affinities of *at least about* 10nM and stronger.

From the reference teachings, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention given the success of Wakai et al and Saxon et al in producing anti-CD23 mAbs that bind to FcgRs and inhibit IgE expression and given the success of Newman et al in producing primatized and humanized versions of anti-CD23 mAbs and disclosing use of compositions containing them as therapeutic agents, particularly in light of the desirability of using such primatized and humanized versions of mAbs as disclosed by Newman et al and Queen et al. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

14. Claim 12 appears to be free of the prior art.

15. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the in the specification.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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September 27, 1999

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